Standard Operating Procedure for Creating and Maintaining an Investigator's Brochure (IB) for UCL Sponsored CTIMPs

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Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JRO/SPON/S03/01	29/10/12	First version	Kim Champion
JRO/SPON/S03/02	30/10/15	Removal of reference to CTC as they now have their own SOP. Minor change of process evidencing IB review.	Kim Champion
JRO/SPON/S03/03	14/02/19	Revision Date Reached	Farhat Gilani
JRO/SPON/S03/04	27/05/22	Minor changes to process, updates to specific considerations and content needed for the IB for ATIMPs	Catherine Maidens

ACRONYMS:	
ATIMP	Advanced Therapy Investigational Medicinal Products
CI	Chief Investigator
CTC	Cancer Research UK & UCL Cancer Trials Centre (UCL affiliated Clinical Trials Unit)
CTIMPs	Clinical Trials of Investigational Medicinal Products
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IP	Intellectual Property
JRO	Joint Research Office https://www.ucl.ac.uk/joint-research-office/
MHRA	Medicines and Healthcare products Regulatory Agency
PV	Pharmacovigilance
RM (ATMP)	Regulatory Manager for ATIMPs
RSI	Reference Safety Information
SI	Statutory Instrument
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UCL	University College London

Standard Operating Procedure for Creating and Maintaining an Investigator's Brochure (IB) for UCL sponsored CTIMPs

1. PURPOSE

This Standard Operating Procedure (SOP) describes the purpose, minimum content, creation, maintenance and/or review of an Investigator's Brochure (IB) used in clinical trials of Investigational Medicinal Products (CTIMPs) sponsored by UCL and managed by the Joint Research Office (JRO).

2. JOINT RESEARCH OFFICE POLICY

All Joint Research Office (JRO) SOPs will be produced, reviewed and approved in accordance with the JRO SOP on SOPs.

The JRO acts as the representative of the Sponsor and will be the official name used on all SOPs.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/28/EC (these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments. Where applicable it incorporates elements of ICH GCP tripartite guidelines (E6).

In addition, for trials with EU and Northern Ireland sites the SOPs will have to be compliant with EU Clinical Trials Regulation No. 536/2014, when applicable.

The IB is a document containing a summary of the clinical and non-clinical data relating to an Investigational Medicinal Product (IMP) which are relevant to the study of the product in human subjects.

The Sponsor of a clinical trial should ensure that the IB for that trial presents the information it contains in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. The Sponsor should validate and update the IB at least once a year.

The IB provides the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial.

The IB contains the Reference Safety Information (RSI) for the IMP against which the expectedness of a suspected serious adverse reaction is assessed by the Sponsor for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and annual safety reporting.

4. SCOPE OF THIS SOP

This SOP covers the procedure for creating and maintaining IBs for IMPs developed by UCL, and used in Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored by UCL. For the purpose of this SOP, UCL developed products refer to therapeutic agents developed by UCL staff and manufactured in a UCL facility or on behalf of UCL.

For IMPs supplied to UCL for use in clinical trials by other drug suppliers, the drug supplier may provide an IB for the IMP being supplied. Drafting of such an IB is outside the scope of this SOP. However, the sponsor should review the supplied IB prior to submission to the MHRA, to check it contains a clearly defined Reference Safety Information (RSI) section (see section 6.2.2).

For an IMP with a marketing approval, where the IMP is being used outside the terms of the marketing authorisation, and no IB has been provided by a drug supplier, it may be necessary in some circumstances to create an IB for use in the clinical trial, instead of referring to the Summary of Product Characteristics (SmPC). In such instances, the procedure in this SOP should be followed.

5. RESPONSIBLE PERSONNEL

The roles and responsibilities of personnel are detailed in the table found in section 6 of this SOP.

6. PROCEDURE

6.1 Drafting of IB

	Task	Responsible Person
6.1.1	Provide Chief Investigator (or person who will author the IB) with the UCL JRO Investigator's Brochure template (associated template). Where necessary refer the CI / IB Author to seek advice from the Pharmacovigilance (PV) Manager.	JRO Sponsor Regulatory Advisor (SRA) / Regulatory Manager for Advanced Therapies (RM (ATMP)
6.1.2	Draft the IB on the JRO UCL IB template. Also refer to ICH GCP E6 (R2), section 7, for guidance on the minimum information that should be included in an IB. In addition, for CTIMPs with Advanced Therapy Investigational Medicinal Products (ATIMPs) the European Commission Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (2019) must be consulted for specific considerations and content needed for the IB including but not limited to: (a) The rationale for the non-clinical development should be discussed and justified, including in cases where the sponsor considers that non-	Chief Investigator (CI) / IB Author

	clinical studies are not feasible. Comprehensive information about the non-clinical development should be provided in the IB. (b) The reconstitution of the ATIMP (where applicable) should be described in the IB. It is acceptable that the detailed instructions are laid down in a separate document available at the site (e.g. handling instructions and/or pharmacy instructions), which can be attached as Annex to the IB. (c)The IB should provide comprehensive information on the risks of the product (based on existing knowledge), including risks associated with the administration procedure and/or upstream interventions on subjects, and information on short and long-term safety issues particular to ATMPs such as infections, immunogenicity/immunosuppression and malignant transformation. (d) Where appropriate, information should be provided in the Protocol and the IB on the measures that should be put in place to protect clinical trial subjects from identified risks. (e) Detailed information should be provided in the IB on the product handling, containment and disposal. It is acceptable that detailed instructions are laid down in a separate document available at the site (e.g. handling instructions and/or pharmacy instructions), which can be attached as Annex to the IB.	

6.2 Review of IB

	Task	**Responsible Person**
6.2.1	Review the IB to ensure inclusion of the required information as per JRO UCL IB template (associated template). *Note:* For IBs not drafted on UCL JRO IB template, ensure they contain at a minimum the main headings stipulated in the JRO IB Template (associated template). *Note:* For IBs provided by a drug supplier, the review can be limited to checking it contains a clearly defined RSI section (see 6.2.2 below).	SRA / RM (ATMP)
6.2.2	Evidenced review of the safety information in the IB to ensure it contains any anticipated side effects from previous clinical studies *(where applicable)*, and the Reference Safety Information (RSI) section is compliant with the Clinical Trial Facilitation Group (CTFG) Q&A document – Reference Safety Information (Nov 2017).	PV Manager
6.2.3	Evidenced review of IB for clinical trials with ATIMP to ensure the additional information as per section 6.1.2 has been appropriately addressed.	RM (ATMP)
6.2.4	*For UCL drafted IBs:* Once the reviews are complete and the IB is finalised send to CI for signature. *For IBs provided by drug suppliers:* Where the JRO review has identified that updates to the IB are required, the CI and the JRO should liaise with the drug supplier to provide an updated version.	SRA / RM (ATMP) CI

	Ensure all reviews are documented in the Sponsor File / Trial Master File (TMF).	
6.2.5	Submission of IB for Regulatory approval for use within the trial as per JRO/SPON/S29 SOP for Obtaining Research Ethics Committee and Clinical Trial Authorisation Approvals for Clinical Trials of Investigational Medicinal Products. Filing and distribution of the approved IB to applicable parties, such as to the CI or directly to the trial sites.	SRA / RM (ATMP)

6.3 Updates to the IB

	Task	**Responsible Person**
6.3.1	*For UCL drafted IBs:* Send reminder to CI to perform an annual review of the IB. The timing of the annual review will usually be in line with drafting the Development Safety Update Report (DSUR), when a safety review of the IMP is performed. *For IBs provided by drug suppliers:* Request an updated version from the drug supplier if one has not been received within the last year (or within the frequency specified in the drug supply agreement). Once received, perform a review (see section 6.3.6 below).	PV Manager
6.3.2	*For UCL drafted IBs:* Perform an annual review, and if applicable, revision of IB. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new clinical or safety information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly the Ethics Committee(s) and/or Regulatory Authority/ies before it is included in a revised IB. The revised/amended IB must contain a revision history in either the IB or a separate summary of changes document indicating the changes that were made to the document. Where the review indicates there is no requirement to revise/amend the IB, the CI should sign a copy of the Annual Review of Investigator's Brochure form (associated template) and the IB version remains the same until next review.	CI
6.3.3	Review of revised and amended safety sections of the UCL IB before release of new version.	PV Manager/ RM (ATMP)
6.3.4	Evidence of all reviews (JRO and CI) must be documented in the TMF and Sponsor File.	SRA / RM (ATMP) / PV Manager

6.3.5	Submission of the revised and amended IB for regulatory and REC approval, as required, as per JRO/SPON/S13 SOP for the Classification, Review and Submission of Clinical Trial Amendments. Filing of the revised and amended IB in the TMF and also in the Sponsor File. Only when approval from the MHRA has been received - Distribution of the newly approved version IB to applicable parties, such as CI or directly to the trial sites can occur.	SRA / RM (ATMP)

7. REFERENCES

ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R2) (2016) https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

Clinical Trial Facilitation Group (CTFG) Q&A document – Reference Safety Information (Nov 2017) https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No 1031), as amended.

COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

Detailed Guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3)

European Commission Detailed guidelines on good clinical practice specific to advanced therapy medicinal Products (2019) https://ec.europa.eu/health/system/files/2019-10/atmp_guidelines_en_0.pdf

9. TEMPLATES/LOGS/SOPS ASSOCIATED TO THIS SOP

1	UCL JRO Investigator's Brochure Template
2	Annual Review of Investigator's Brochure Form

10. SOP DISSEMINATION AND TRAINING

This SOP will be distributed to the relevant JRO staff. Staff will sign the SOP training log (12. SOP TRAINING LOG) which is part of each SOP.
The training will constitute of the person reading the SOP and being provided with the opportunity to ask specific questions to the author of the SOP.

11. SIGNATURE PAGE

Author and Job Title	Catherine Maidens, Pharmacovigilance Manager
Signature:	DocuSigned by: Catherine Maidens 6A859A9CF4FB497...
Date:	27 April 2022 | 14:32 BST
Authorised by: Name and Job Title	Helen Cadiou, Head of QA
Signature:	DocuSigned by: Helen Cadiou 9FE319AE9B744D5...
Date:	27 April 2022 | 09:56 BST

12. SOP TRAINING LOG

	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	I confirm that I understand & agree to work to this SOP **SIGNATURE**	**Name of Trainer (**if training required)	**Signature**	**Date**
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	I confirm that I understand & agree to work to this SOP **SIGNATURE**	**Name of Trainer (**if training required)	**Signature**	**Date**
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